Clinical Overview of Ovarian Cancer and the Potential Role of Molecular Imaging

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Objectives

- Clinical Overview of Ovarian Cancer
- Unmet need for high resolution imaging of the peritoneal cavity
- Potential role of molecular imaging in ovarian cancer

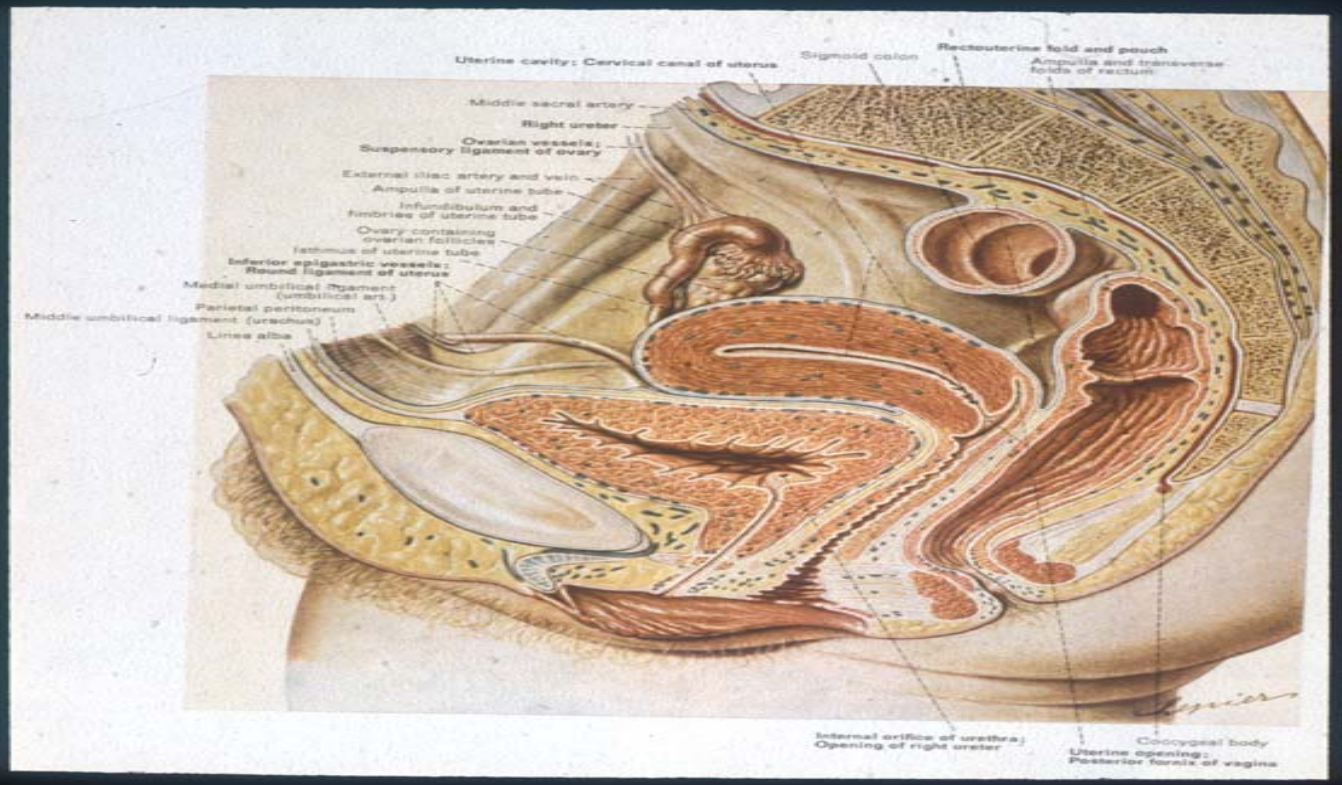
Age-adjusted cancer death rates
Females, by site, US, 1930-1992

Ovarian Cancer

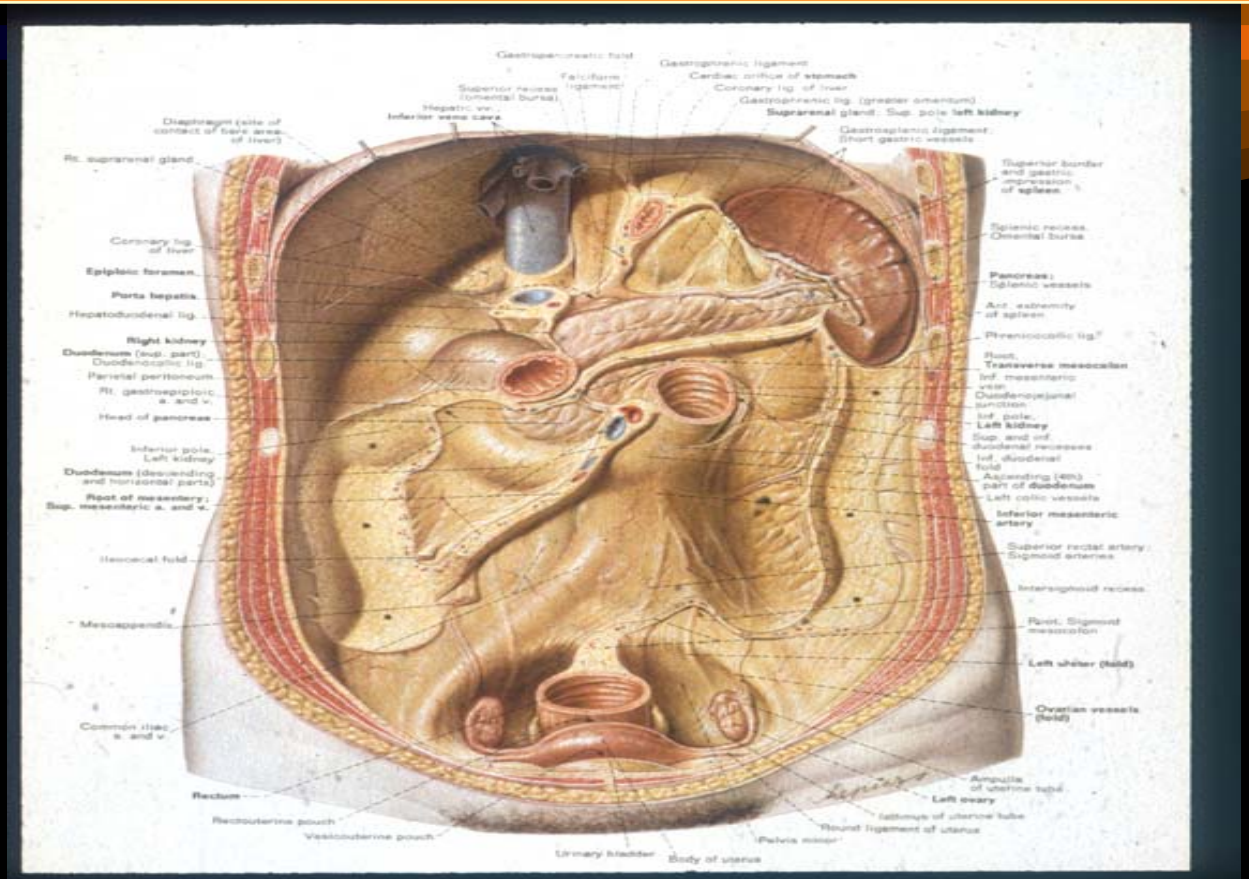
- Tumors arise on the surface or near the surface of the ovary. Primary tumors are typically asymptomatic
- No effective screening tool is available
- Diffuse peritoneal spread is common
- The majority of women present with extensive regional disease with bulky peritoneal disease

Clear Cell Carcinoma of the Ovary

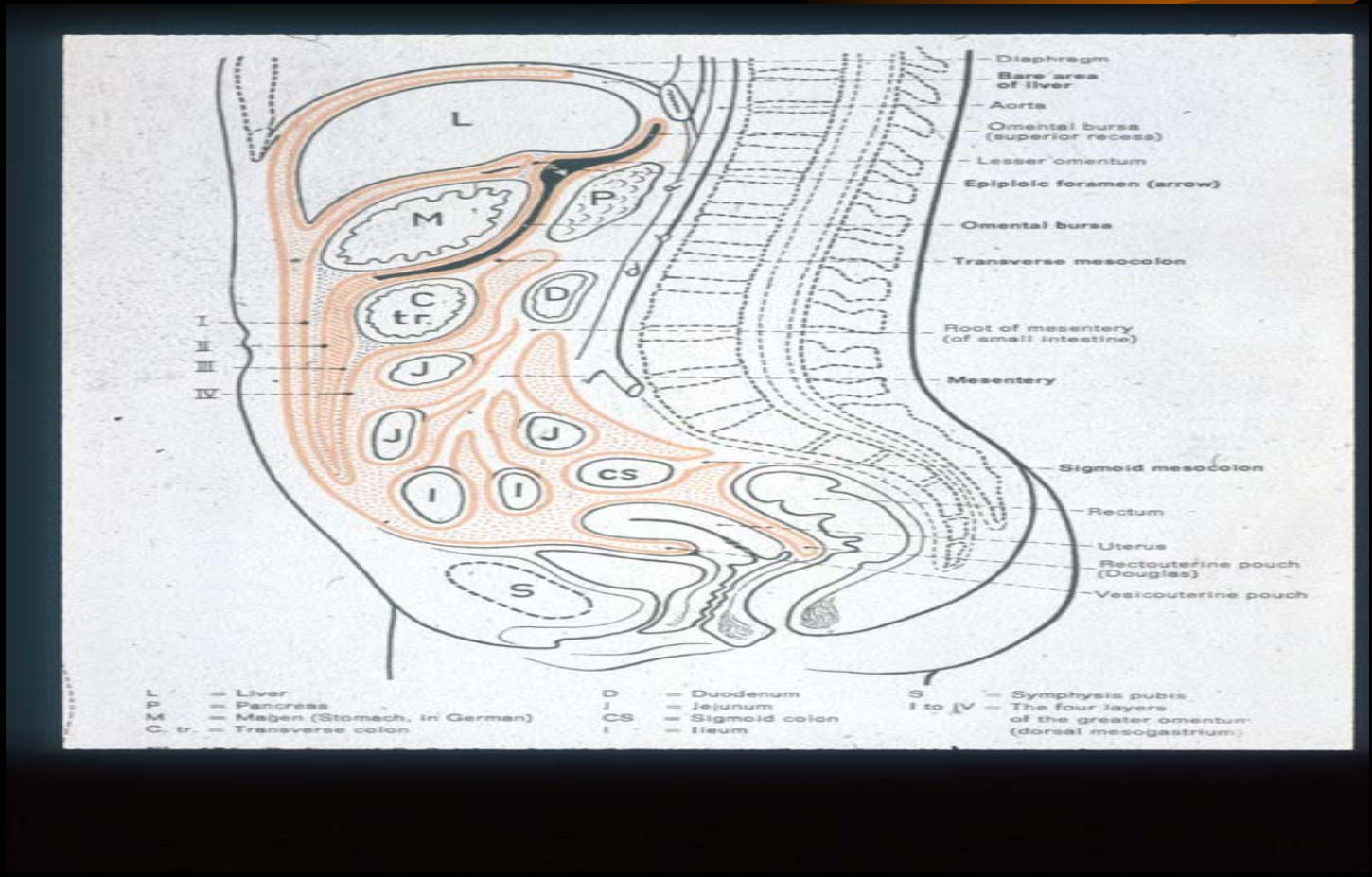
Cross section of the Female Pelvis

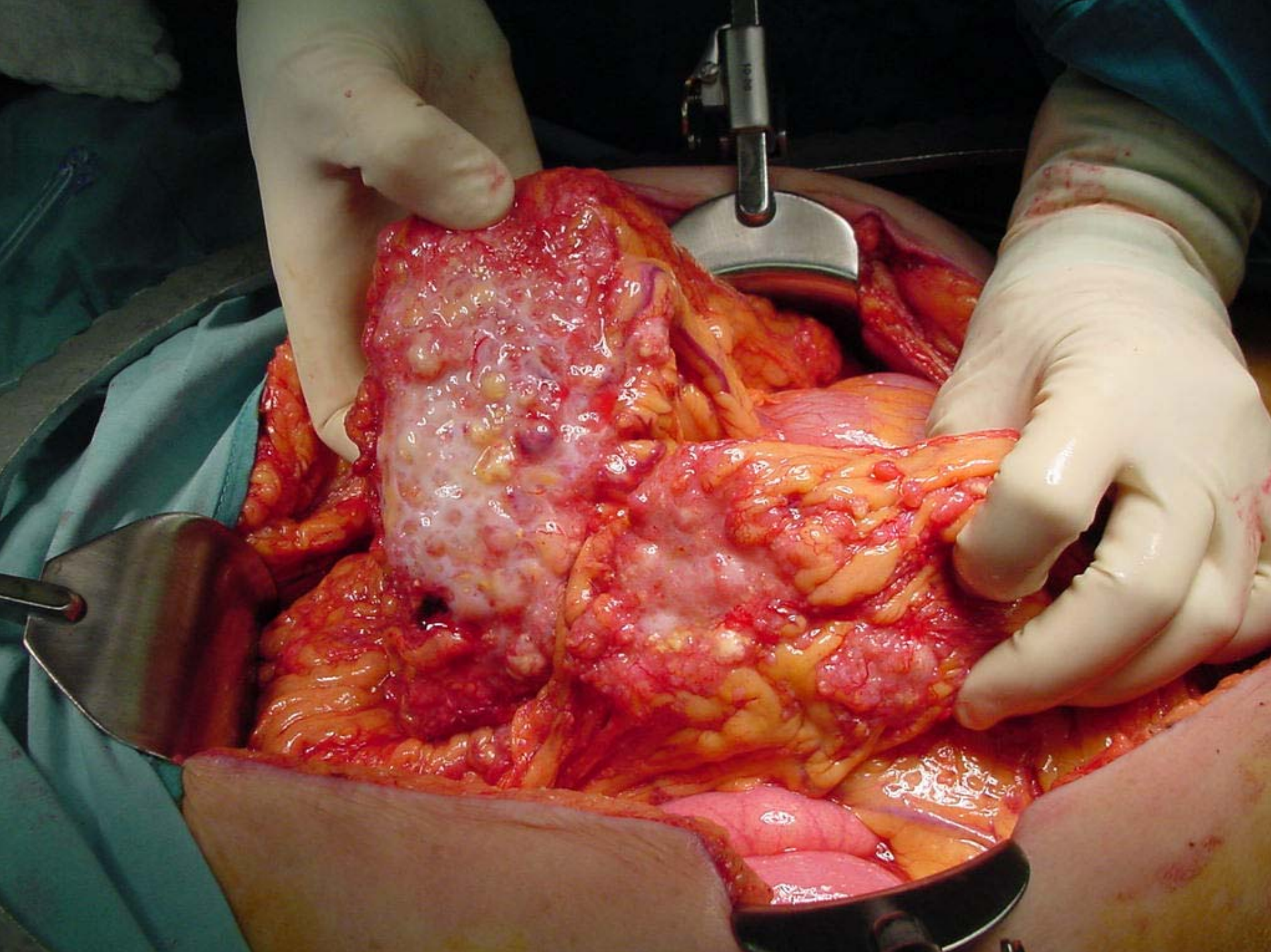


Female Abdominal Cavity

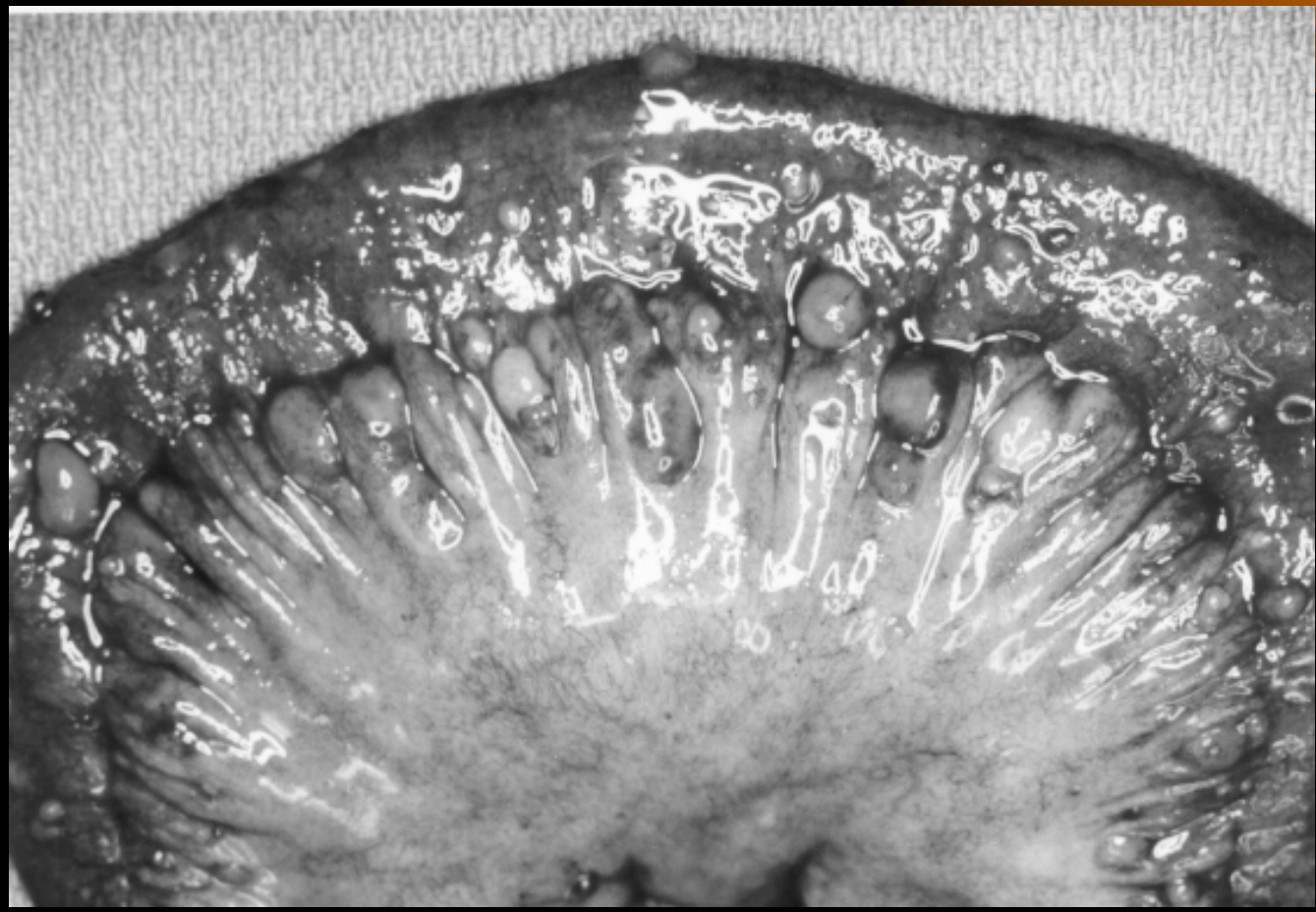


The Abdominal Cavity has a Massive Surface Area





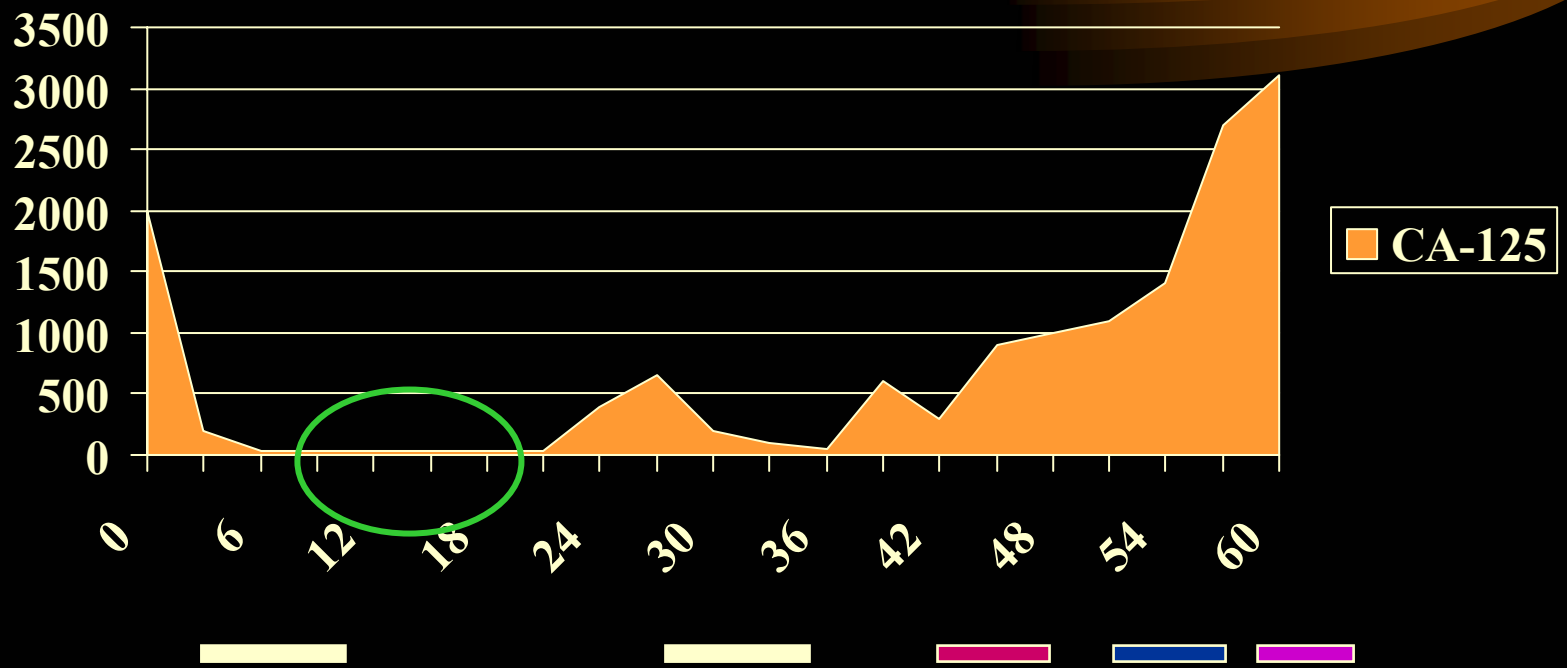
Development of Bowel Metastases



Therapy for Newly Diagnosed Ovarian Cancer

- Surgery-Typically removes in excess of 99% of the tumor
- Chemotherapy may remove an additional 99% of residual tumor
- The majority of women will be in a clinical remission after chemotherapy
- Clinical remission is not synonymous with cure

Natural History of Epithelial Ovarian Cancer

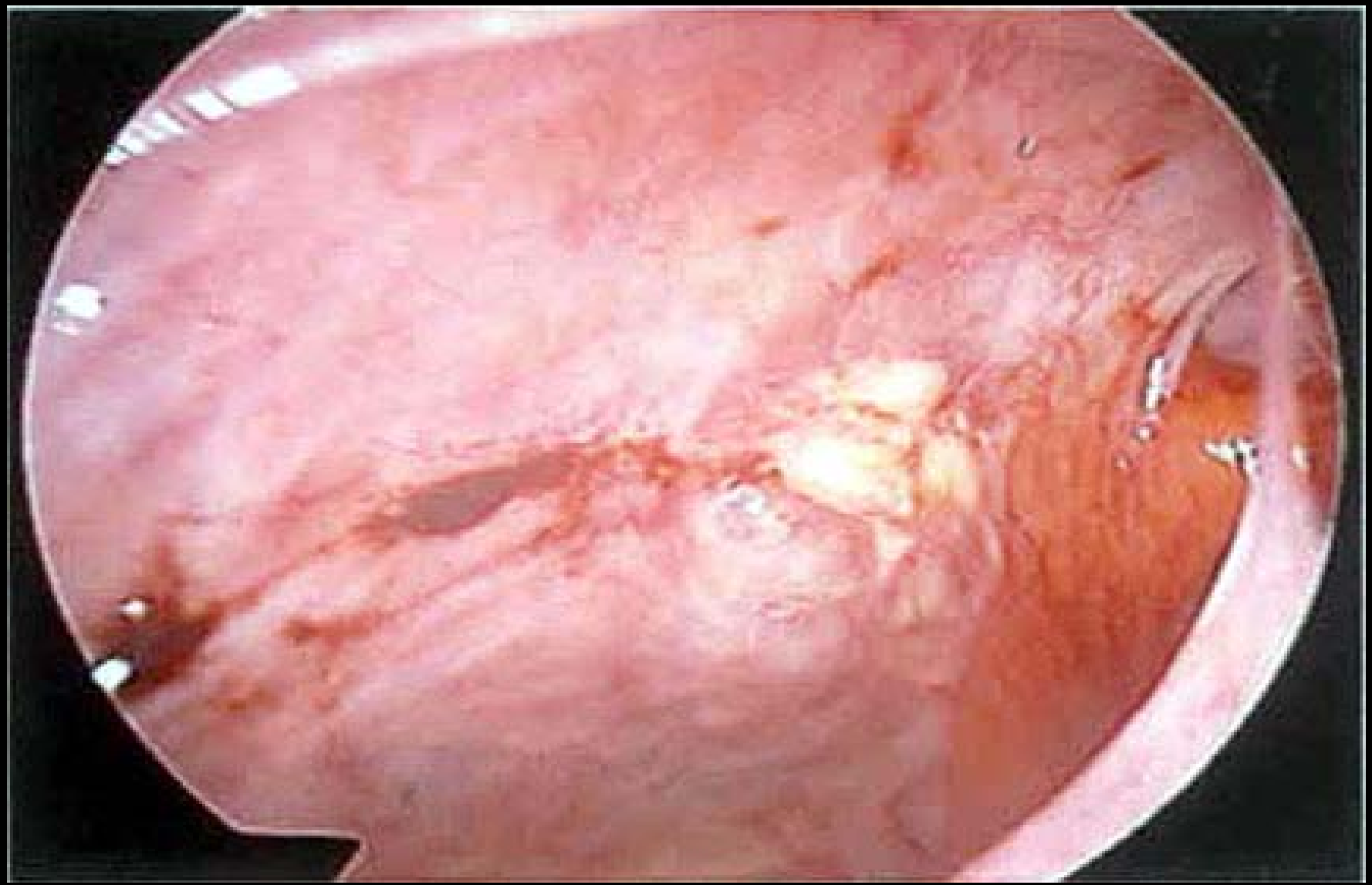


Chemotherapy's

Normal Peritoneal Surface

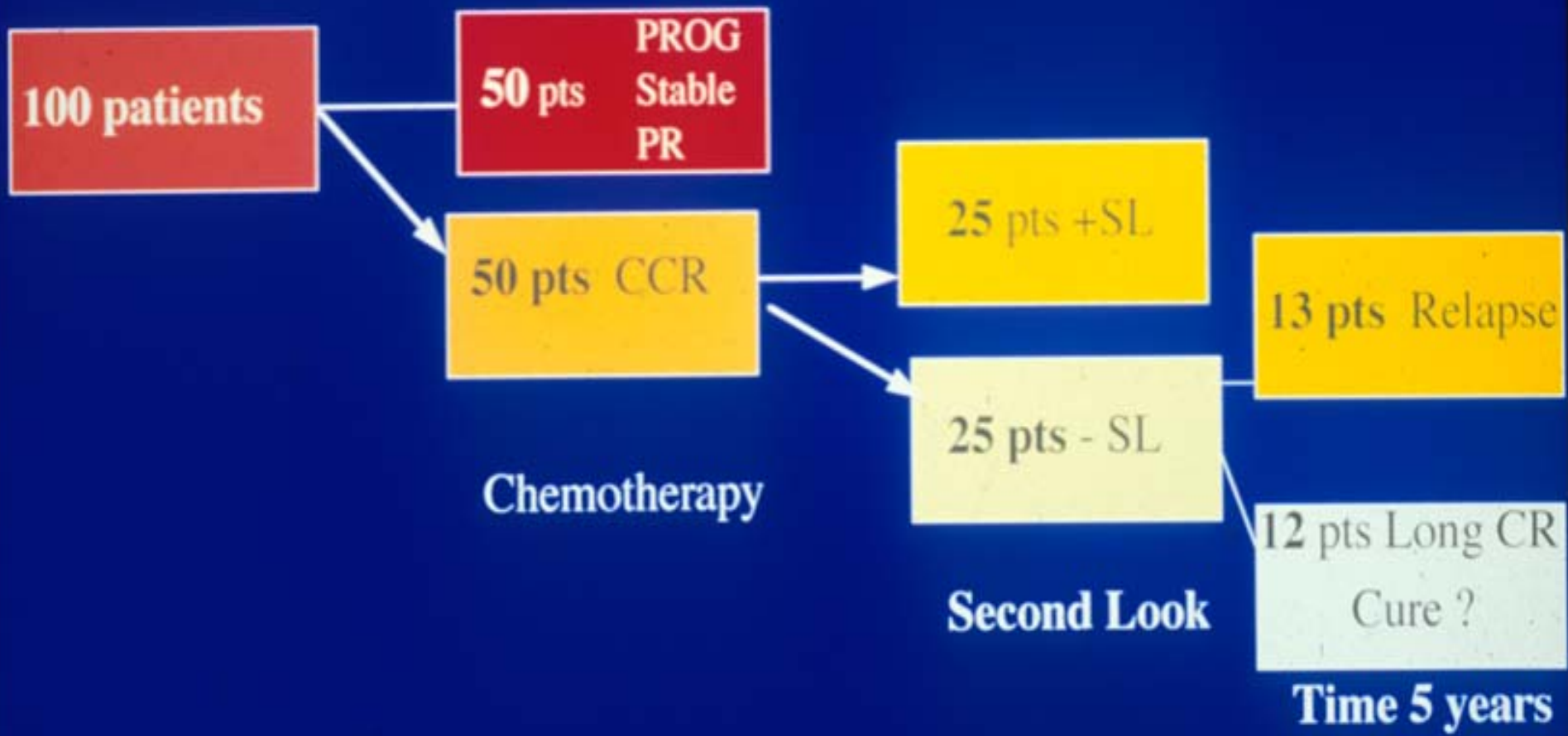
Abdominal Wall Tumor Implants

Diaphram Metastases



Ovarian Cancer

- Patient Outcomes-Stage IIIc/IV Disease



Ovarian Cancer:Agents in Development

- **Tubulin Binding Drugs**- Taxol analogs, epothilones, other tubulin binders
- **VEGF Inhibitors-Bevacizamab**
- **EGFR Inhibitors**-Irresa, CI-1033, EMD 72000, OSI-774 (Tarceva), C225 (Irbitux)
- ***Ras-RAF Pathway Inhibitors***- *Bay 43-9006*

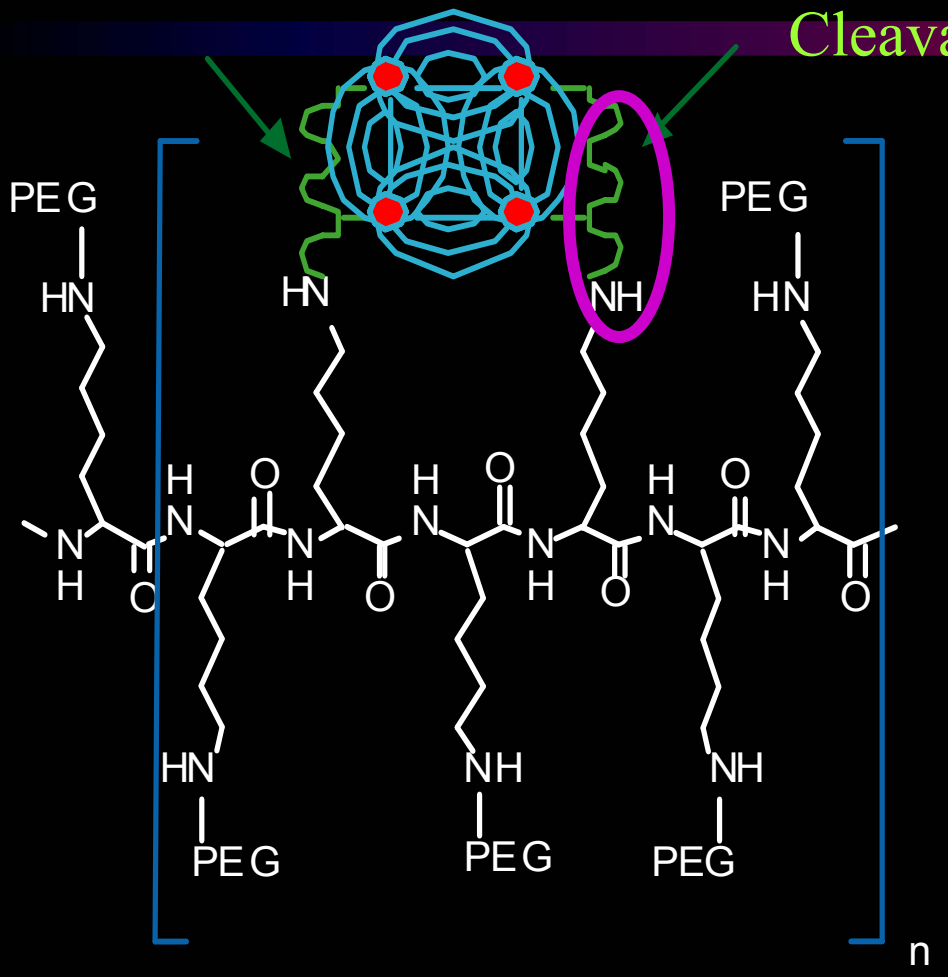
Role of molecular imaging in ovary cancer

Hypothesis - Technologies that identify and characterize key biologic functions in very small volume ovarian cancer would provide important prognostic and therapeutic information

Other Imaging Modalities

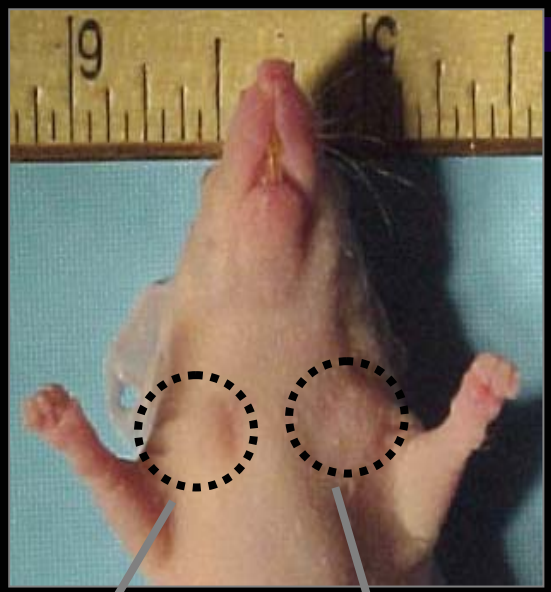
- CT scan-Difficult to visualize peritoneal disease < 1 cm
- MRI-a bit better in evaluating tumor in pelvis but less sensitive in the abdomen
- PET-Good at visualizing retroperitoneal and pelvic nodes but insensitive in detecting tumor fixed to mobile bowel.

Biocompatible in vivo probes

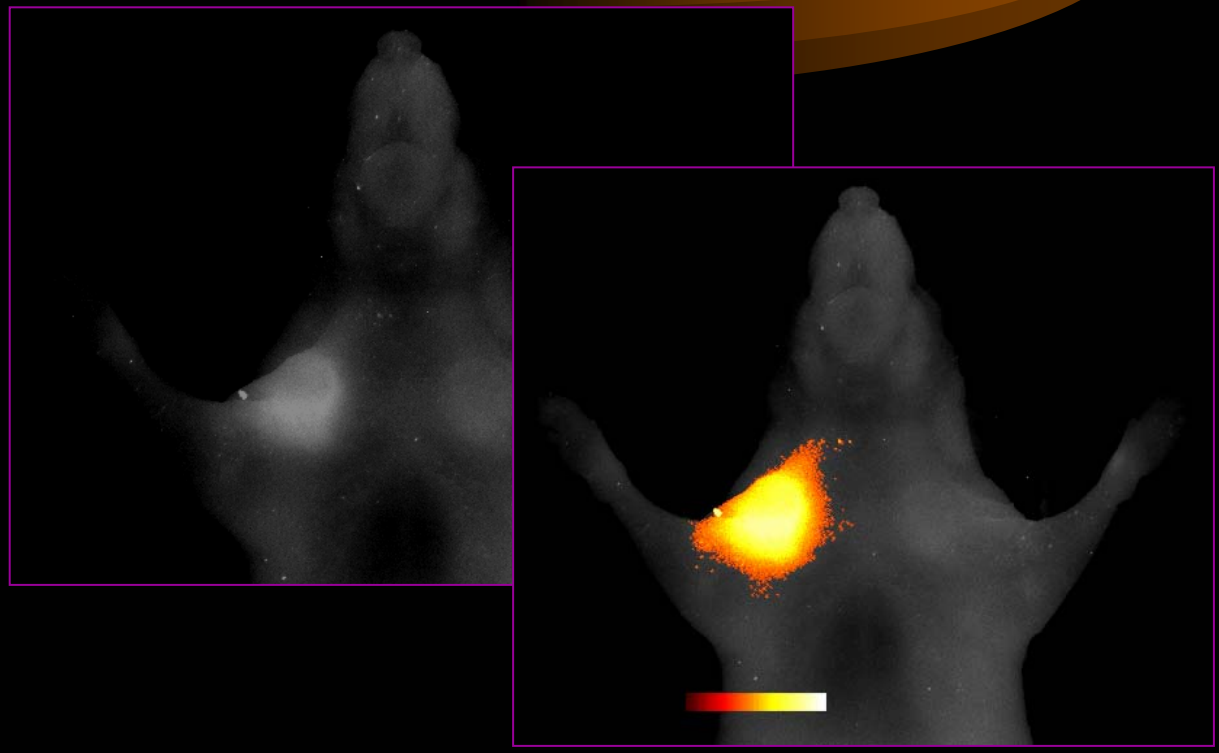


- NIR fluorescence
- High NIRF loading
- High quenching
- High release rates
- Specificity

In-vivo imaging of MMP-2 activity

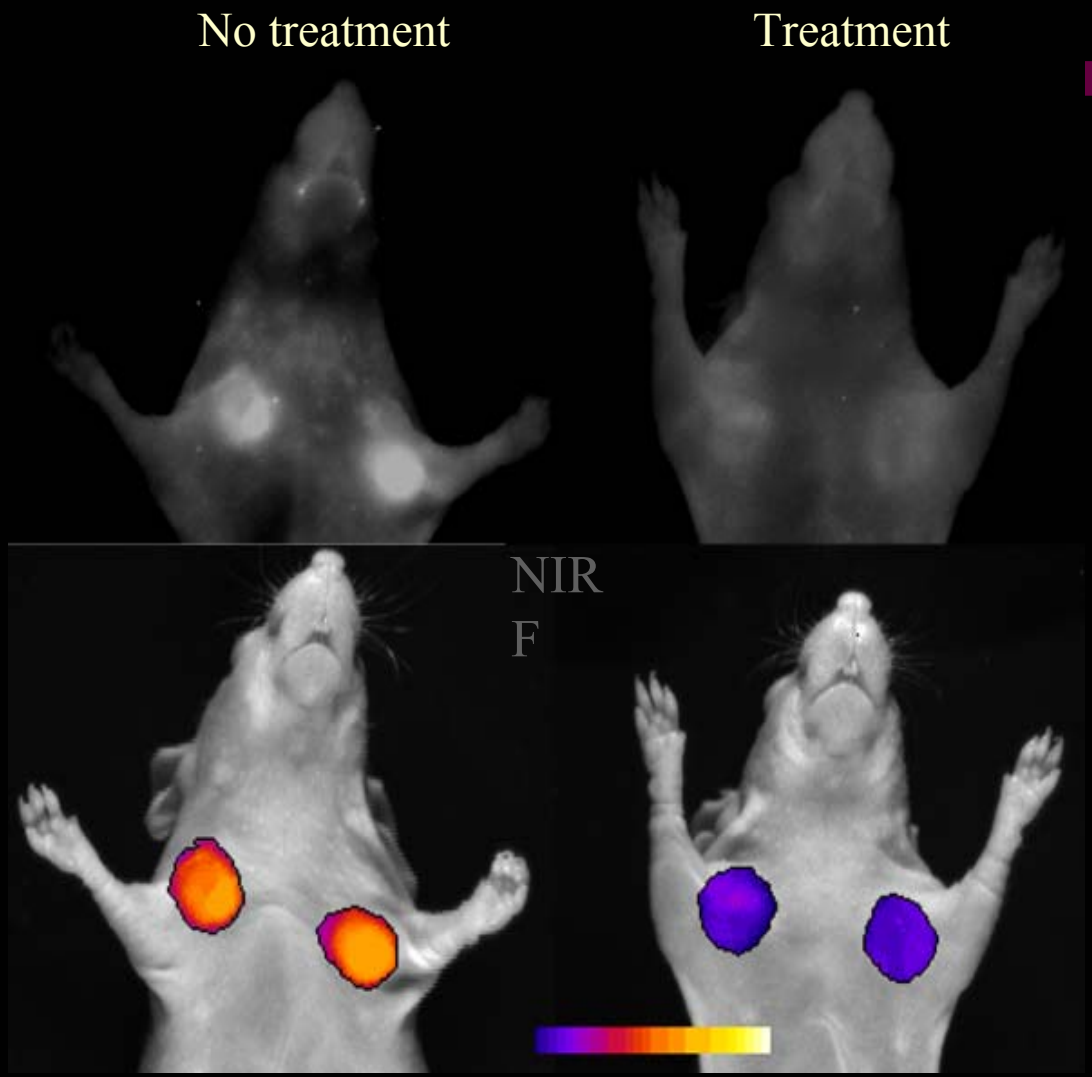


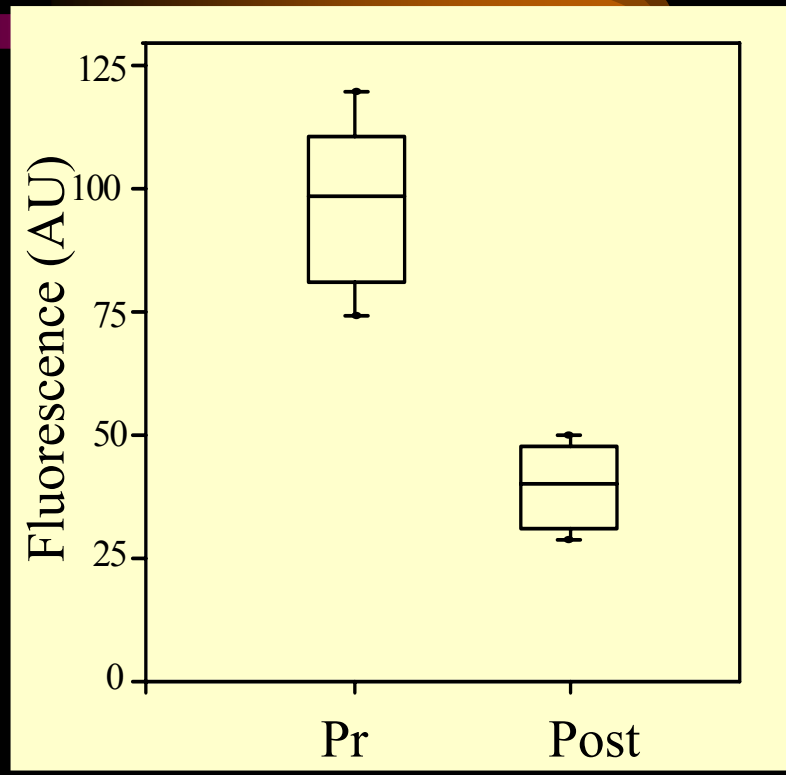
MMP2 + **MMP2 -**



MMP2 + **MMP2 -**

MMP-2 inhibitor treatment





Inhibitor 100 mg bid IP x 2 days

Weissleder et al., MGH-CMIR

Goals of a Molecular Imaging Program for Ovarian Cancer

- Goals
  - Patient Goals
  - Physician Scientist Goals
  - Pharmaceutical / Biotechnology Goals
- Requirements
  - Probe requirement
  - Sensor requirement

Intra-peritoneal molecular imaging: Patient Goals

- Improve survival and quality of life by:
  - Avoiding clinically ineffective and toxic therapies
  - Selecting best therapies at best dose at best time

Intra-peritoneal molecular imaging: Physician Scientist Goals

- Characterize key biologic functions in tumor nodules
- Evaluate the effect of therapeutics on these key biologic functions in real time and *in situ*
- Early detection of drug resistant tumors with elucidation of the mechanisms of therapeutic failure

Intra-peritoneal molecular imaging:
Pharmaceutical/ Biotechnology Consideration

- Unmeet clinical research need
- Provides biologically based model for selecting “best” lead compounds for clinical testing in Phase II trials
- Leads to “biologically-based” dosing strategies and evaluation of novel therapeutics

Requirements (1)

Detects a biologic process (the imaging agent)

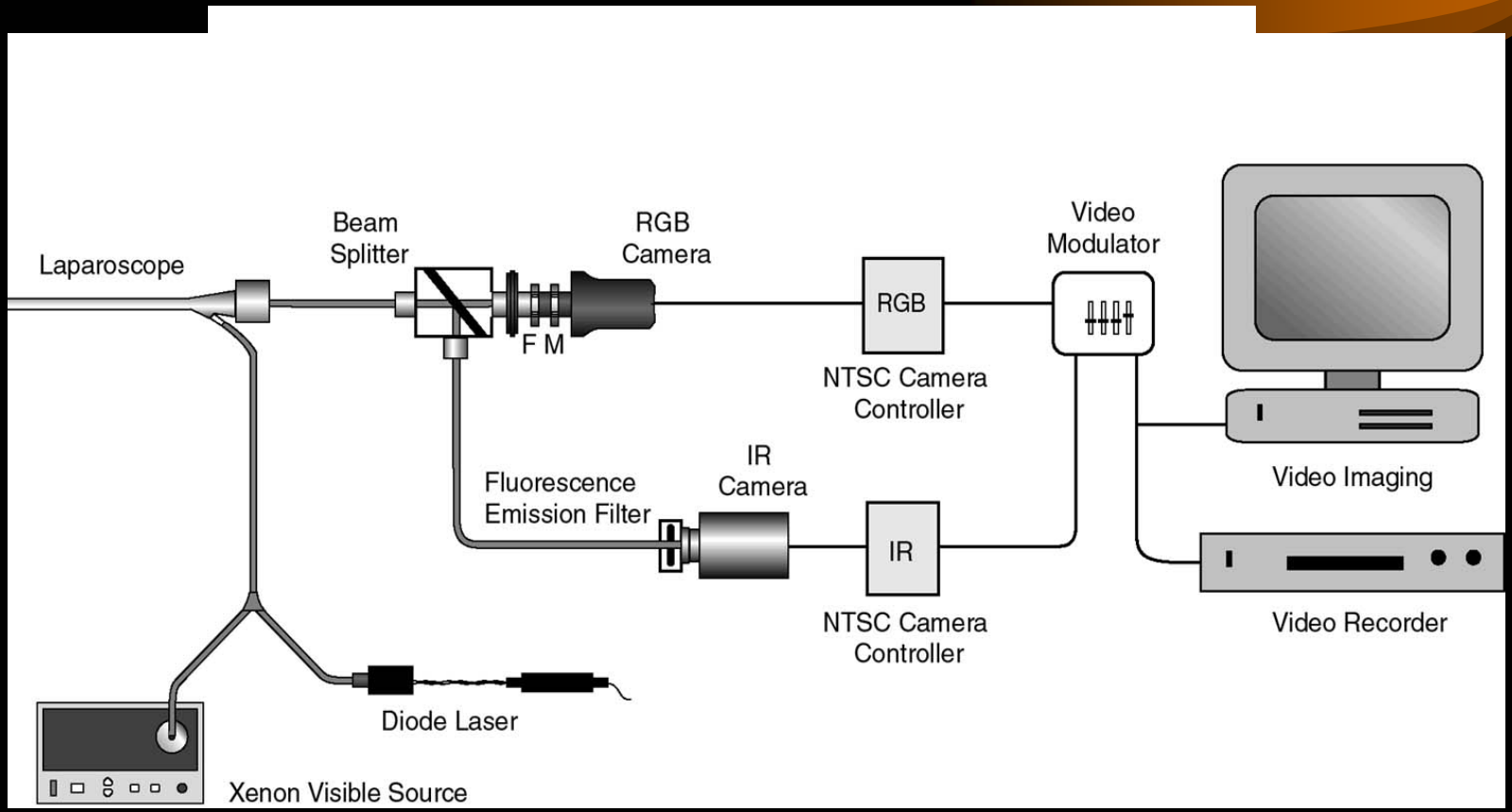
- Ideally not a drug
- Must measure biologically important process
- Must be deliverable to all tumor cells with high efficiency
- Must discriminate (quantitate) over 2 or 3 logs of activity

Requirements (2)

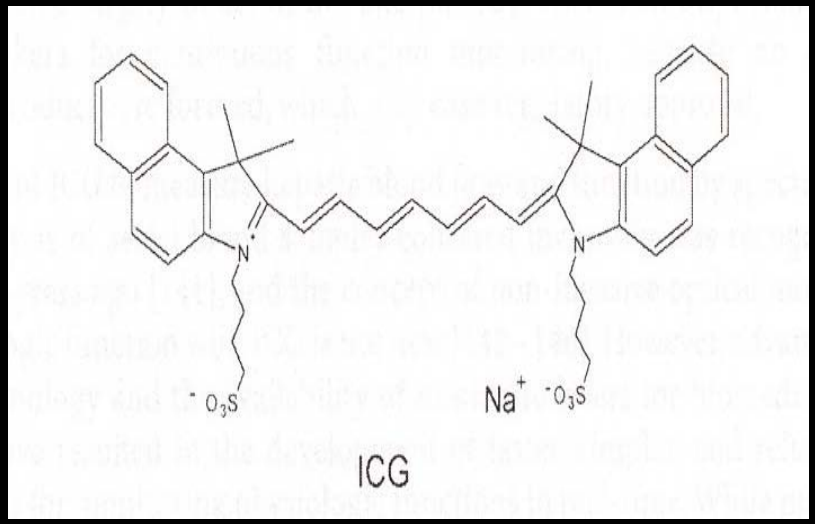
Measures the biologic process (The sensor)

- Measures mm or sub-mm lesions in Real Time
- Must be capable of detecting and quantitating signals over several logs of intensity
- Must be suitable for sequential measurements
- Minimally invasive

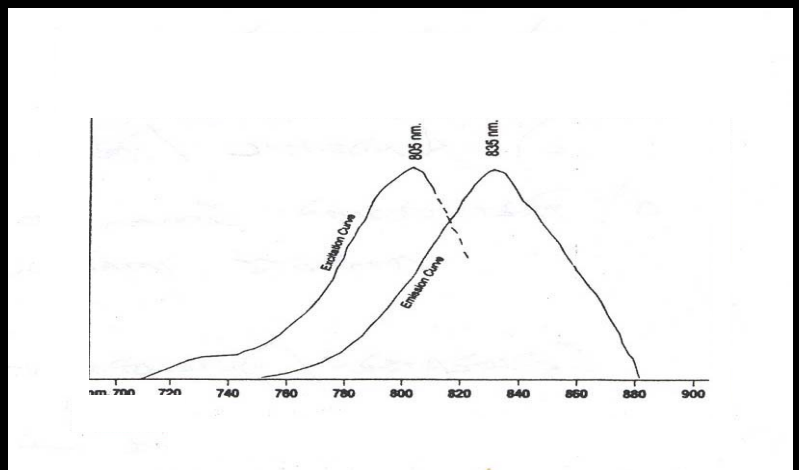
Near Infrared Laparoscope



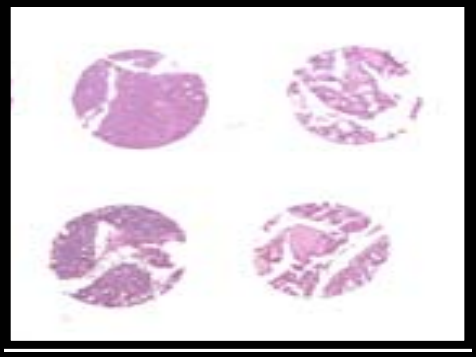
ICG as a clinically available NIRF

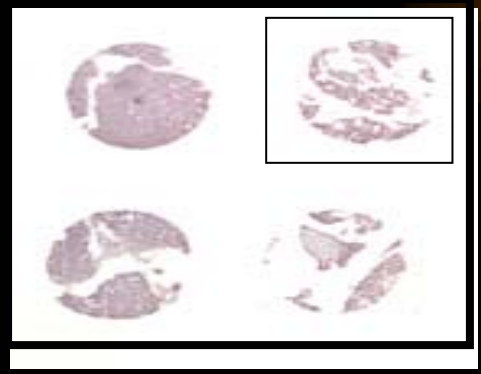


- Used in opthalmic angiography
- Very limited toxicity
- PK well defined



Validation of NIRF probe is important





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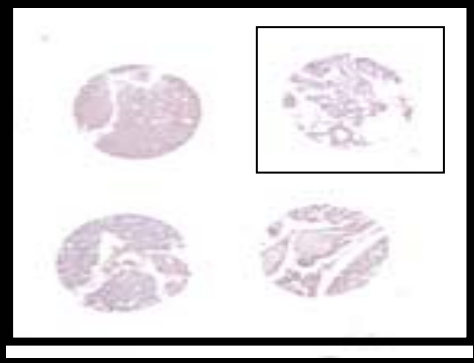

Final Conclusion

- The combination of the frequency of ovarian cancer, inferiority of current imaging technologies, and the treatable but seldom curable nature of ovarian cancer makes this malignancy a logical choice for the development of molecular imaging efforts in the next decade.

Acknowledgements

- MGH
  - Richard Penson
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